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Presumed Severe Hepatocellular Toxicity after Initiation on a Dolutegravir-Based HIV Treatment Regimen in Rural Malawi: A Case Report

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Abstract

Dolutegravir-based regimens are quickly becoming the preferred anti-retroviral therapy of choice in sub-Saharan African countries. Dolutegravir-based regimens are highly effective and well tolerated, however there are reports of adverse effects including drug induced liver injury. A case report of a 45-year-old male living with HIV who developed symptoms of liver damage two months after initiating a dolutegravir-based antiretroviral regimen. We believe that drug induced liver injury was the possible source of his liver failure secondary to dolutegravir, which highlights the need for early clinical recognition, laboratory monitoring and mechanisms for clinicians to prevent and diagnose early drug induced liver injury in resource-limited, rural settings.

Keywords: DILI; Dolutgravir; DTG; Liver injury

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Introduction

As Sub-Saharan Africa countries progress towards the goal of universal anti-retroviral therapy (ART) coverage with viral suppression amongst their cohorts, dolutegravir (DTG) has been adopted as first line treatment for human immunodeficiency virus (HIV) infections. DTG is an integrase strand transcriptase-inhibitor, which is highly effective, has a high barrier to resistance, well tolerated, and is an acceptable formulation to patients [1-6]. Additionally, in the last few years DTG-based formulations have become more affordable for low and middle-income countries [7,8]. Despite its effectiveness in treating HIV, DTG has several notable adverse effects (AE). For example, hepatic injury, was demonstrated during the experimental stage of DTG development [6,9,10]. *In vitro*, there are 4 mechanisms by which ART could cause liver toxicity: 1) direct drug toxicity on the liver metabolism; 2) immune reconstitution syndrome; 3) hypersensitivity reactions; and 4) mitochondrial toxicity [11]. Across the world, there have been several reports of drug induced liver injury (DILI) as a result of DTG alone or in combination with other ART [12-17]. In order to rapidly identify and manage potential DILI from ARTs, adequate laboratory infrastructure, pathology and imaging services are necessary [10,18]. However, in resource limited-settings, health care providers may not have access to the tools to rapidly recognize, diagnose and treat such AE. Therefore, many cases of AE of medications like DTG may go unrecognized, undiagnosed and unreported. Here we present a case of severe liver injury, believed to be secondary to DTG use, in Neno District, Malawi, reviewed through lens of limited diagnosis and management of drug-related adverse events in resource-limited settings.

Case Presentation

A 45-year-old male HIV positive, with no other significant medical history, was hospitalized 3 months after beginning a combined ART regimen of tenofovir, lamivudine and dolutegravir. He complained of 2 weeks of fever, non-productive cough, yellowing of his eyes, night sweats, shortness

of breath, and general body weakness. The patient denied vomiting, dark urine, diarrhea, discolored stools, itching, edema and loss of motor or sense functions. The patient denied smoking, use of alcohol, acetaminophen, or drugs other than the ART and cotrimoxazole 960 mg prophylaxis prescribed during his last visit. He was the father of 5 children and denied a history of recent travel. On admission the patient was sick appearing.

His vital signs included a temperature of 37.7°C, a heart rate of 124 beats per min, a blood pressure of 130/81 mmHg, respiratory rate of 18 breaths per min and a Glasgow coma score of 15/15. His weight was 61 kg with a body mass index (BMI) of 18.8 m^2/kg. Physical examination of his head and neck revealed pale conjunctiva and scleral icterus. His abdomen was soft with positive bowel sounds without distention but tender in the right upper quadrant (with deep palpation) with palpable hepatomegaly (size measurement not reported). The remainder of the examination was unremarkable including respiratory, cardiovascular, and central nervous system.

Laboratory investigations on admission can be seen in Table 1. Pertinent findings include anemia, thrombocytopenia. The Liver Tests (LT) showed a transaminitis with elevated.

Lactate dehydrogenase (LDH), direct bilirubin and gamma glutamine transferase (GGT) levels. The computed R-value between alanine aminotransferase (ALT) and alkaline phosphatase (ALP) was greatly elevated at 22.5, with an ALT/LDH ratio of 0.2. For infectious disease screening hepatitis B surface antigen (HBsAg) was negative. He was not screened for other types of viral hepatitis due to lack of availability of testing. His HIV viral load was not assessed, but his CD4 count was 261 cells/microliter. Investigations for tuberculosis were negative (Table 1). Urine L-arabino mamman (LAM) was negative. Focused assessment with sonography for HIV-associated tuberculosis (FASH-TB) [19] was unremarkable.

At that time, he was diagnosed with liver failure with concern for a DILI type hepatocellular due adverse drug reaction to DTG. The patient's ARV regimen was switched from DTG-based regimen to a combined regimen of tenofovir 300 mg, lamivudine 300 mg, and efavirenz 600 mg (TDF/3TC/EFV). At day two of hospitalization, he had persistent tachycardia (100 bpm to 130 bpm), altered mental status and hypotension (systolic BP of 70 mmHg). His creatinine and urea worsened significantly (Table 1). Unfortunately, in our setting there was no option for liver biopsy or transplant. His condition continued to deteriorate on day 4 with persistent hypotension, hypoglycemia (random blood glucose at 29 mg/dL), low oxygen saturation of 90% on room air and severely altered mental status. The patient died on day 4 of hospitalization.

Discussion

In patients with liver disease the patterns of abnormalities in

Table 1: Laboratory data.

Variable	Variable Abbreviation (if applicable)	Reference Range	On Presentation	Day 2 of hospitalization	Day 4 of hospitalization
Red Blood Cells	RBC	4.35-5.6x10^6/µL	2.23 × 10^6	3.19 × 10^6	
Hemoglobin	Hb	Male - 12-16 g/dL	6.4	9.5	-
Hematocrit	Hct	35-45%	-	27.6	-
Mean Corpuscular Volume	MCV	80-100 fL	71	86	-
White Blood Cells	WBC	4000-10000/ µL	2600	2700	-
Lymphocytes	LYMP	20-40 %	42.3	41.4	-
Polymorphonuclear neutrophils	PMN	50-70 %	36.5	10.1	-
Mixed cells	MXD (monophils, basophils, eosinophils)	N/A	21.2	48.5	-
Platelets	PLT	145000-450000 per µL	71000	41000	-
Sodium	Na+	135-150 mmol/L	-	-	-
Potassium	K+	3.5-5.5 mmol/L	-	-	-
Chloride	Cl−	86-100 mmol/L	-	-	-
Bicarbonate	HCO3−	22-28 mmol/L	-	-	-
Creatinine	Cr	<1.4 mg/dL	-	2.29	4.29
Blood Urea Nitrogen	BUN	10-50 mg/dL	-	89.4	147.7
Asparagine Transaminase	AST	<37 U/L	491	-	-
Alanine Transaminase	ALT	<42 U/L	162	-	-
Alkaline Phosphatase	ALP	64-306 U/L	878	-	-
Total protein		6.6-8.7 mg/ mg/dL	6.8	-	-
Total bilirubin		<1 mg/ mg/dL	16,7	-	-
Direct bilirubin		0.5-0.5 mg/dl	13	-	-
Lactate Dehydrogenase	LDH	140-280 U/L	2454	-	-
Gamma-GlutamylTransferase	GGT	0-41 U/L	50	-	-
Hepatitis B Surface Antigen	HBsAg	Positive/Negative	Negative	-	-
CD4 Cell Count	CD4	>200 cells	261	-	-
Urine-Lipoarabinomannan Assay	Urine-LAM	Positive/Negative	Negative	-	-
GeneXpert on TB sputum		Positive/Negative	Negative	-	-

Table 2: Considerations for acute liver failure etiology.

Category with general pattern	General pattern	Etiology for Acute Liver Failure	Common features or examples
Infection	Can be hepatocellular, cholestatic or mixed	Hepatitis A virus	Hyperacute presentation, more common in older patients or with
			Underlying liver disease
		Hepatitis B virus	Less common hyperacute presentation
		Hepatitis E virus	Higher risk with exposure to farm animals and pregnant women
		Herpessimplex virus	Occurs in immunocompromised patients
		Tuberculosis	More common in immunocompromised patients
		Invasive amoebiasis	Less common and with circumscribed mass on ultrasound
Drugs	Can be hepatocellular, cholestatic or mixed depending on offending agent	Idiosyncratic reactions	Isoniazid, nonsteroidal anti-inflammatory drugs, carbamazepine
		Dose-dependent hepatotoxicity	Acetaminophen, sulfonamides, tetracycline
		Herbal supplements	Need to ask explicitly
Vascular diseases	Hepatocellular	Right heart failure	Likely will need echocardiogram to diagnose
		Budd-Chiari	May have subacute presentation
		Ischemic hepatitis (shock liver)	Ischemia must be prolonged (as with sepsis)
Toxins	Hepatocellular	*Amanitaphalloides* toxin	Rare and difficult to diagnose
		Bacilluscereus toxin	Foodborne transmission
Metabolic diseases	Hepatocellular	Wilson disease	Most common in younger-patients with Coombs-negative hemolytic anemia, hypouricemia and low alkaline phosphatase level with high bilirubin
		Reye syndrome	Occurs in young children with viral syndrome and salicylate ingestion
Malignant infiltration	Cholestaticor mixed	Metastatic breast cancer	Most common solid organ metastasis to cause liver failure
		Lymphoma	More common than leukemic infiltration
Autoimmune diseases	Hepatocellular	Autoimmune hepatitis	Rare cause and difficult to diagnose without antibodies

LT can be suggestive of the underlying etiology: Hepatocellular, cholestasis or mixed. The R-value is computed and used to determine which pattern of LT abnormalities. When the R-value is less than 2, the pattern is suggestive of a cholestasis, while values of more than 5 is suggestive of hepatocellular injury, and values between 2 to 5 is considered mixed hepatocellular and cholestatic injury [20]. Hepatocellular damage is most commonly seen in viral hepatitis, autoimmune hepatitis, toxin-mediated hepatitis, fatty liver disease, vascular diseases associated with chronic heart failure and hereditary liver diseases. Cholestasis is mostly commonly caused by malignancy, granulomatous diseases like tuberculosis or sarcoidosis, abscess due to amoebic or bacterial infections, but can also been seen as a consequence of medications. In addition, LT abnormalities could present a mixed pattern as seen in drug toxicity, malignancy and viral causes.

In our presented case the R-value was suggestive of hepatocellular type injury but laboratory and imaging capacity was limited to rule out additional differential diagnoses. For our patient, hepatocellular injury could have resulted from a chronic viral hepatitis, which could be exacerbated by the introduction of his ARV regimen. It has been reported that pre-ART elevated transaminases, inflammatory and coagulation markers are linked with severe hepatotoxicity with initiation of some ART regiments [21], but not all of these tests available for our patient. However, the ratio of ALT/LDH of 0.2 in our patient was less suggestive of viral hepatitis despite being done following initiation of DTG [22].

Diffuse hepatic involvement by tuberculosis during pulmonary or miliary TB is also a possibility. Essop and Al reviewed 96 cases of tuberculosis with hepatic involvement and reported findings that are similar to our case [23]. Such presentation is not unusual for tuberculosis [24] but less likely with negative urine LAM and negative sputum examination on GeneXpert along with negative FASH-TB exam. Tuberculosis of the liver most often presents with an infiltrative enzyme pattern characterized by elevated ALP and normal ALT and aspartate transaminase (AST) levels. Toxin-mediated causes are also suggested by an R-value greater than 5 [25]. Toxicology testing was not available in our setting, but the only toxin we were able to determine that our patient was exposed to was the DTG-based regimen. The pattern of LT disturbances seen in our case could also have resulted from an autoimmune process, although autoimmune hepatitis presents most commonly as a chronic transaminitis and higher transaminases [26]. Autoimmune markers are important to exclude autoimmune hepatitis as differential diagnostic but were not available.

Ultrasound imaging is useful to establish some etiologiesof liver failure with reduced cardiac output could be the cause of subsequent liver shock or congestive hepatopathy [27-29]. The presence of upper quadrant pain is not uncommon in advanced congestive cardiac-liver [28]. Although, in such cases, the liver dysfunction is superimposed on existing chronic heart failure [30]. Additionally, ultrasound imaging can be useful in ruling out parasitic infection as etiology of LT abnormalities. It has been shown in prior studies that HIV infection may increase the likelihood of invasive amoebiasis including amebic liver abscess [31,32]. Although the LT abnormalities in invasive

amoebiasis shows an infiltrative pattern and well-defined hypo echoic mass in ultrasonography [21,33,34].

Elevated ALP and weight loss could raise the suspicion of malignancy, since males are at high risk for liver malignancy and exposure to important risk factors like aflatoxins in Malawi cannot be overlooked [35-38]. Solid liver lesions like malignant tumors are ruled out by imaging and when positive, a liver biopsy is needed for the definitive diagnostic [17,39,40].

It is recommended that biopsy, liver function tests and other laboratory tests with radiological imaging to establish the diagnosis of liver failure, but do not always confirm the etiology [41,42]. In our setting, there is limited diagnostic capability to allow for direct diagnosis. Our case represents a challenging but not uncommon scenario of diagnostic uncertainty, but this case had features to suggest DILI due to DTG toxicity. We relied on clinical exam findings and few laboratory capacities to indicate DILI as the possibleetiology. The ratio of ALT/LDH of 0.2 was suggestive of drug toxicity [22]. An elevated direct bilirubinemia and AST as seen in our case are highly suggestive of DILI [29]. Previously reported cases of DILI secondary to DTG present with similar history, clinical findings and LFT disturbances similar to the case presented here [12]. DILI is the impairment of the liver's synthetic function [21] and differs pathologically from injury caused by alcohol, viruses or autoimmune reactions (Table 2). In a case with suspicion of DILI, it is paramount to identify the causal agent, and to stop its use before more advanced complications. The Naranjo adverse drug reaction probability score and the Roussel Uclaf Causality Assessment Method (RUCAM) score are used to establish the direct association with the offending drug [12,43-46]. Our case is representative of many cases of DILI in resource-limited settings with high R-value, acute onset of symptoms and no other history suggesting other etiology. However we were constrained by lack of diagnostic testing at both ARV initiation and the acute liver failure. It reflects the ambiguity and challenges in establishing a diagnosis in light of substantial limitations in available diagnostics [47].

Conclusion

We report a case of fulminant liver failure that was presumed to be DILI due to DTG liver toxicity. In resource limited settings where a lack of pre-treatment LFTs or chronic hepatitis is not routine, clinicians should remain aware of the possibility of DILI even with drugs with a history of excellent hepatic safety records like DTG. This case emphasizes the need for routine pre-ART liver function tests and further laboratory and imaging modalities if required within standard recommendations to prevent DILI during country-wide transitions to DTG based regimens.

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